Oral Rifampin and Trimethoprim/Sulfamethoxazole Therapy in Asymptomatic Carriers of Methicillin-Resistant *Staphylococcus aureus* Infections

RICHARD T. ELLISON III, MD; FRANKLYN N. JUDSON, MD; LYNN C. PETERSON; DAVID L. COHN, MD, *and* JOSEPHINE M. EHRET, *Denver*

During a hospital outbreak of methicillin-resistant Staphylococcus aureus *(MRSA) disease in 30 patients we studied the use of rifampin and trimethoprim/sulfamethoxazole (TMP/SMX) in managing asymptomatic carriers. The outbreak persisted despite control measures including "barrier" precautions, screening cultures, identification of affected persons and rapid hospital discharge of affected patients. The MRSA strain was susceptible to both rifampin and TMP/SMX and in vitro the combination was not antagonistic. Fourteen carriers received a five-day course of rifampin and TMP/SMX given by mouth. Twelve patients were evaluable. Cultures remained persistently positive in four patients, three of whom had foreign bodies that could not be removed. Among the eight with an initial response, two relapsed to the carrier state more than six months after treatment. During the study the outbreak resolved. These data suggest that rifampin and TMP/SMX may decrease the number of MRSA-colonized patients, but may not permanently eradicate the MRSA carrier state.*

(Ellison RT III, Judson FN, Peterson LC, et al: Oral rifampin and trimethoprim/sulfamethoxazole therapy in asymptomatic carriers of methicillin-resistant *Staphylococcus aureus* infections [Clinical Investigation]. West J Med 1984 May; 140:735-740)

Since 1974 methicillin-resistant *Staphylococcus aureus* (MRSA) has been increasingly recognized as both a nosocomial and a community-acquired pathogen in the United States. By 1981 it had been identified in at least 109 United States hospitals and there were 24 published outbreaks.[1-4] Fortunately, adequate treatment of MRSA infection is usually possible with vancomycin hydrochloride, which appears to have an efficacy comparable to that of β-lactam antibiotics in the treatment of methicillin-sensitive *S aureus* infections.[5,6] However, there has been little success in controlling the spread of MRSA; the infections continue to occur in more than 85% of US hospitals that have recognized the pathogen.[7]

Epidemiologic studies of nosocomial MRSA outbreaks suggest that patients are the major hospital reservoir for the organism. In recent investigations slightly more than 50% of patients who have carried MRSA strains have had clinical infection.[7] The remaining noninfected colonized patients represent a silent reservoir for further nosocomial spread. While three outbreaks have been related to chronic nasal carriage by individual hospital workers, during outbreaks of MRSA infections the prevalence of MRSA carriage in hospital employees with patient care responsibilities has averaged only 2% of those tested; this suggests that this group is only a minor reservoir for the pathogen.[7] MRSA has been cultured from inanimate objects in

From the Disease Control Service, Denver Department of Health and Hospitals, and the Division of Infectious Diseases, Department of Medicine, University of Colorado Health Sciences Center, Denver.

Submitted, revised, February 6, 1984.

Reprint requests to Franklyn N. Judson, MD, Disease Control Service, 605 Bannock Street, Denver, CO 80204.

ABBREVIATIONS USED IN TEXT

MIC = minimal inhibitory concentration
MRSA = methicillin-resistant *Staphylococcus aureus*
SMX = sulfamethoxazole
TMP = trimethoprim

hospitals, but such colonization has been implicated neither in spreading the pathogen nor in maintaining the organism in the environment.[1,3,7-9]

Epidemiologic observations of nosocomial MRSA have noted roommate-to-roommate and bed-to-adjacent-bed spread.[7] Transient hand carriage of MRSA strains after contact with colonized or infected patients has been documented and this may be an important mode of patient-to-patient spread.[7-9]

Recommended measures to prevent nosocomial MRSA transmission have included surveillance cultures to identify colonized and infected patients, use of "barrier precautions" to isolate infected or colonized patients and rapid discharge from hospital of infected or colonized patients when it is medically feasible.[10]

Ward and his associates reported that a regimen effective in eradicating colonization with MRSA was (1) topical bacitracin ointment three times a day for five days, (2) hexachlorophene baths during the initial two days and (3) rifampin (300 mg) given by mouth twice a day for five days with or without trimethoprim/sulfamethoxazole (TMP/SMX) 80 mg/400 mg twice a day for five days.[11] In this study we report our in vivo and in vitro observations on the efficacy of combined oral rifampin and TMP/SMX therapy alone in eradicating colonization with MRSA during an apparently typical outbreak at a city hospital.

Patients and Methods

Denver General Hospital is a 300-bed facility serving mainly indigent patients in the Denver metropolitan area. The hospital has 56 medical beds, 126 surgical beds, 52 pediatric beds, 35 obstetric-gynecologic beds and 60 psychiatric beds. There are four intensive care units (one medical, one surgical, one combined medical-neurosurgical and one pediatric). There were 16,294 hospital admissions in 1982. An outbreak of MRSA disease was first recognized in August 1981 and this report includes all patients and personnel subsequently identified who had one or more cultures positive for MRSA.

Methicillin-resistant *Staphylococcus aureus* cases were identified through review of all clinical microbiology laboratory isolates and by surveillance cultures carried out on personnel and patients having direct contact with known cases. Cultures of specimens from anterior nares, wounds and other potentially infected sites were done. Cases were classified as either infection or colonization on the basis of history, physical examination, laboratory studies and clinical course.

Bacteriologic Methods

MRSA isolates were identified by compatible colony morphology and Gram's stain, a positive coagulase test and resistance to oxacillin by the disc diffusion technique of Kirby-Bauer.[12,13] Surveillance cultures were done on mannitol salt agar. Bacteriophage typing was carried out on an isolate from each case by the Centers for Disease Control, Atlanta.

Antimicrobial Susceptibility Testing

Isolates from each case were stored at −70°C in trypticase soy broth with 15% glycerol. Rifampin diagnostic powder was obtained from CIBA Pharmaceutical Co (Summit, New Jersey) and sulfamethoxazole and trimethoprim from Hoffmann-LaRoche, Inc (Nutley, New Jersey). Minimal inhibitory concentrations (MIC) to rifampin, TMP, SMX and combinations of rifampin, TMP, TMP/SMX and rifampin/TMP/SMX were determined by an agar dilution method using Sensitest agar (Oxoid, Columbia, Maryland) containing 5% lysed horse erythrocytes. Inocula of 0.003 ml were delivered by multipoint inoculator using overnight cultures in Mueller-Hinton broth diluted to an inoculum of 100,000 colony-forming units per ml.[14,15] Plates were incubated for 24 hours at 35°C. The MIC was defined as the lowest concentration of antibiotic at which no growth occurred. Activity of rifampin was tested with serial twofold dilutions from 25 to 0.003 μg per ml, TMP with twofold dilutions from 1.6 to 0.003 μg per ml and SMX with twofold dilutions from 31.2 to 0.03 μg per ml.

Time-kill curves with rifampin, TMP/SMX and rifampin/TMP/SMX were carried out with one isolate of MRSA. Studies with selected antibiotic concentrations were done using 100,000 colony-forming units per ml of MRSA in Sensitest broth (Oxoid) containing 5% horse erythrocytes. Aliquots were removed at 0, 4, 24 and 48 hours and incubated overnight at 35°C.

Control Measures

All patients identified as being either colonized or infected with MRSA were placed in private rooms with "gown-and-glove precautions." The responsible physicians were encouraged to discharge the patients as soon as it was medically indicated and their charts were prominently labeled for rapid recognition during subsequent clinic visits or hospital admissions. The one employee colonized with MRSA who remained at the hospital was removed from patient care while colonized.

After November 1981 the patients and employee colonized with MRSA were treated with rifampin, 600 mg given twice a day by mouth, and TMP/SMX, 160 mg/800 mg given twice a day by mouth, for five days. Any removable foreign bodies (urethral catheters, endotracheal tubes, intravenous catheters) were replaced on the third day of therapy. Follow-up cultures of all colonized sites were done in each treated patient.

Results

Between August 1981 and May 1982 a total of 29 patients and one employee were identified as being

colonized or infected with MRSA (Figure 1). No new cases were identified in the subsequent six months and, for the purpose of this study, the outbreak was considered to be "controlled." In all, 28 of the patients and the one employee were found to have bacteriophage type 53/83A/85+. The remaining patient had MRSA of indeterminate bacteriophage type isolated from a foot ulcer on his initial visit to the hospital and was felt to have a community-acquired organism that was not part of the outbreak. This outbreak was epidemiologically typical of nosocomial outbreaks of MRSA reported previously.[1-7]

The characteristics of the cases were similar to those described by others (Table 1). These patients had very prolonged hospital stays and tended to acquire the MRSA late in their hospital course after receiving numerous antibiotics. Of the patients, 6 were infected and 22 were colonized. Two infected patients (33%) died of MRSA infection while six colonized patients (27%) had unrelated deaths. Of the first 12 cases, 10 occurred on one general surgical service and in the other 2 early cases the patients were in the same hospital unit as patients from this service. MRSA subsequently became endemic in the surgical and joint medical-neurosurgical intensive care units and then involved patients on other surgical services. Transmission of the organism most commonly occurred from roommate to roommate, apparently on the hands of personnel. During the outbreak ten colonized patients were readmitted to either this hospital or another facility, although no secondary cases arising from contact with these patients were identified. Two patients had their first culture for MRSA noted immediately on readmission following a hospital admission during the outbreak period. One of these two admissions occurred in a hospital in another state.

Surveillance cultures were carried out on 87 hospital personnel who had patient contact and 23% were found to be colonized with methicillin-sensitive *S aureus*. The outbreak strain of MRSA was found in cultures from two of the personnel, one who had persistently positive cultures from eczematous skin and a second who left the facility before follow-up cultures could be done to ascertain that they were persistently positive. Neither of these employees was present at the onset of the outbreak, nor could they be directly implicated in the spread of the pathogen.

The MRSA strain had a consistent antibiogram during the outbreak with disc diffusion tests showing sensitivity to gentamicin, amikacin and vancomycin and resistance to penicillin, oxacillin, tobramycin, clindamycin, erythromycin and tetracycline. Fifteen of the initial isolates were tested for TMP, SMX and rifampin MICs. All were sensitive to TMP (0.2 μg per ml) and SMX (3.9 to 7.8 μg per ml). Whereas all were sensitive to rifampin, 12 of the isolates had an MIC of 0.003 μg per ml or less and three obtained late in the outbreak had an MIC of 0.1 μg per ml. Antagonism between rifampin and TMP/SMX was not found in ten strains tested by a checkerboard technique.

From December 1981 through May 1982 there were 14 MRSA-colonized patients and personnel who received 17 courses of an oral regimen of rifampin and TMP/SMX (Table 2). Two patients were not available for follow-up; one died of his underlying illness one day after completion of the regimen and the other was discharged from hospital and did not return. Of the remaining 12 patients, 4 had positive cultures for MRSA within ten days of the end of therapy. Three were retreated with the five-day regimen and two again had positive cultures within three days. One had nasal MRSA colonization and multiple facial bone fractures

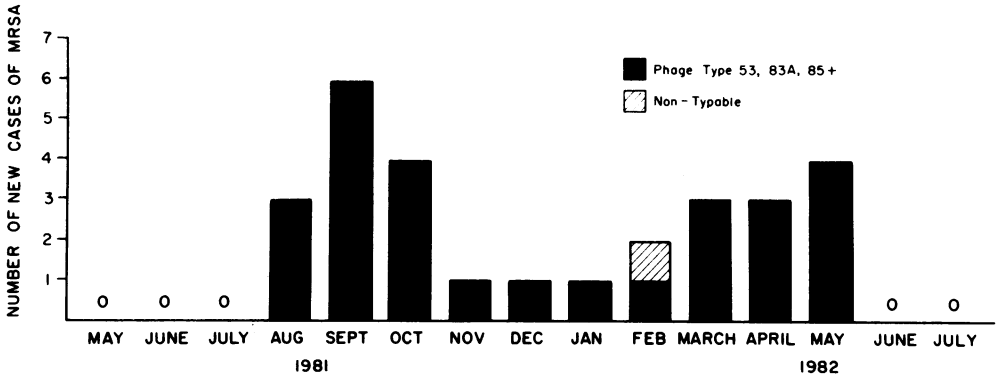

Figure 1.—New cases of methicillin-resistant **Staphylococcus aureus** (MRSA) colonization or infection, August 1981 through May 1982.

TABLE 1.—*Characteristics of Patients Colonized or Infected With Methicillin-Resistant* Staphylococcus aureus *53/83A/85+*

	Mean ± Standard Error	*Range*
Age (years)	51.8± 4.1	20 to 86
Total duration of hospital stay (days)	72.1±10.4	6 to 196
Interval from admission to first isolate (days)	38.3± 5.1	6 to 89
Number of different antibiotics received before first isolate	4.2± 0.1	0 to 9
Number of patients colonized	22	
Number of patients infected	6	

stabilized by interosseus wires and the other persistent sputum colonization in association with obstructing squamous cell lung carcinoma at the carina. Among eight patients with negative initial follow-up cultures, two had negative cultures for MRSA within the first month after treatment but then had cultures positive for the epidemic strain six and nine months after treatment. Neither of these patients was known to have had new contact with MRSA. In none of the remaining six patients could new cultures be done more than a month after the completion of the rifampin/TMP/SMX therapy, four patients had died and two were lost to follow-up.

No patient had an adverse reaction to the three-drug regimen. However, the one patient in whom the therapy failed and who was not re-treated with the five-day regimen received the three drugs inadvertently for 18 days. In this patient an asymptomatic aminotransaminase elevation developed that resolved and then recurred after a single dose of rifampin.

Paired MRSA isolates before and after therapy were available in three patients in whom the therapy failed. The patient who had interosseus wires in place was treated twice and there was a successive rise in rifampin MIC from 0.003 or less to 0.1 to 0.8 μg per ml although there was no change in TMP or SMX susceptibility. In the patient who received prolonged therapy there was a rise in rifampin MIC from 0.003 or less to more than 25 μg per ml, again without changes in TMP or SMX susceptibility.

Time-kill curves of the activity of rifampin, TMP/SMX and rifampin/TMP/SMX were carried out with the initial isolate from the patient with interosseus wires in place in whom therapy failed. The isolate was tested in the presence of presumed serum concentrations of the antibiotics (rifampin 1 μg per ml, TMP 1 μg per ml and SMX 20 μg per ml) and rapid killing occurred with all combinations (Figure 2). The isolate was then tested using concentrations of antibiotics that were twice the in vitro MICs, 0.006 μg per ml for rifampin and 0.5/1.0 μg per ml for TMP/SMX. At these antibiotic concentrations not only was rapid resistance to rifampin demonstrated, but TMP/SMX did not prevent the emergence of rifampin resistance (Figure 3).

Discussion

Optimal management of a persistent carrier of *S aureus* has yet to be defined. Studies of the natural history of nasal *S aureus* carriage show that multiple staphylococcal strains may be present concurrently and fluctuate as to relative numbers.[16] Predominant strains can persist for as long as 21 years.[16] Attempts to control nasal staphylococcal carriage with topical antibiotic ointments have succeeded in decreasing the numbers of staphylococci present, but not in their eradication.[17] The replacement of a pathogenic staphylococcal strain with a supposedly nonpathogenic strain, *S aureus* 502A, has been found to aid in controlling nosocomial outbreaks and recurrent furunculosis, but its usefulness has been limited by both the need for repetitive instil-

TABLE 2.—*Outcome of Oral Rifampin/Trimethoprim/Sulfamethoxazole Therapy in 13 Patients and One Employee Colonized With Methicillin-Resistant* Staphylococcus aureus *(MRSA)*

Patient Number	*Underlying Illness*	*Colonization Site(s)*	*Posttherapy Culture Results* (day of culture)*	*Comment(s)*
2	Lung carcinoma	Sputum	4+; re-treated, 1+, 3+, 6+	Bronchial obstruction with carcinoma
7	Cholangiocarcinoma	Nose, bile	1−, 11−, 33−	Biliary drainage tube
10	Abdominal gunshot wound	Sputum, abdominal wound	15−, 35−	Concurrent vancomycin therapy for MRSA bacteremia
14	Basilar skull fracture	Sputum	1−, 2−, 3−, 4−	Tracheostomy
15	Pelvic fracture	Abdominal wound	2−, 6−, 17−, 29−, 60−, 274+	Recurrent MRSA noted 9 months after therapy
17	Cervical spine gunshot wound, quadriplegia	Sputum	6−, 10−	
18	Peripheral vascular disease	Abdominal wound	2−, 4−	Unrelated death 6 days after treatment
19	Automobile accident, facial bone fractures	Nose, sputum, facial wound	2+, 5+, 25+, 27+, 40+; re-treated, 3+, 57+, 83+	Interosseus wire fixation of fractures
20	Subdural hematoma	Nose, sputum, ankle decubitus	Not cultured	Unrelated death 1 day after treatment
22	Lung carcinoma	Nose, sputum, axilla, groin	2−, 8−	
23	Hidradenitis suppurativa	Perineal skin graft	3−, 10+; re-treated, 3−, 61−	
24	Subdural hematoma	Nose, sputum	1+, 6+, 26+	Tracheostomy, not re-treated with 5-day regimen
25	Abdominal wall abscess	Abdominal wound	Not cultured	Discharged from hospital without follow-up cultures
28	Employee	Eczematous hand lesions	2−, 140+, 154+	Recurrent MRSA noted 6 months after therapy

*+ indicates isolation of MRSA, − indicates no growth of MRSA (for example, 4− indicates no growth of MRSA on cultures obtained on fourth day after therapy).

lations to suppress the pathogenic strains and the finding that this strain is itself occasionally pathogenic.[18-20] Studies in volunteers have shown that macrolide antibiotics given by mouth can decrease the intensity of nasal staphylococcal carriage and that rifampin given by mouth can temporarily eliminate it, but controlled studies of their clinical utility in persistent staphylococcal carriage have not been done.[21-23] Further, the use of rifampin as a single agent has not been advocated because of concern over the possibility that rifampin resistance would rapidly emerge.

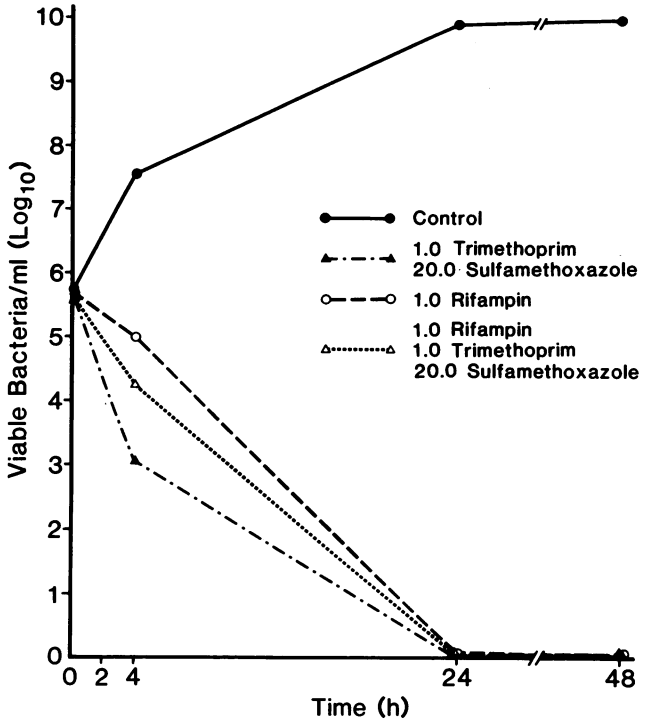

Figure 2.—Activity of rifampin, trimethoprim/sulfamethoxazole and rifampin/trimethoprim/sulfamethoxazole against an isolate of methicillin-resistant *Staphylococcus aureus* at expected serum concentration of the antibiotics.

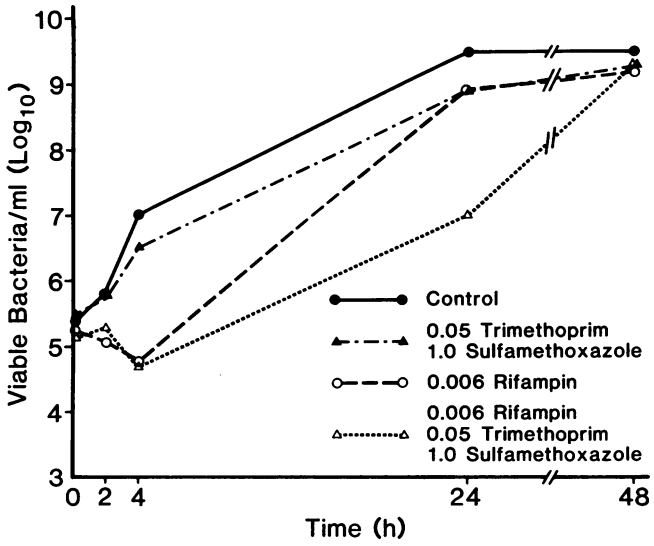

Figure 3.—Activity of rifampin, trimethoprim/sulfamethoxazole and rifampin/trimethoprim/sulfamethoxazole against an isolate of methicillin-resistant *Staphylococcus aureus* at twice the in vitro minimal inhibitory concentration of the antibiotics.

Ward and co-workers reported that a regimen of topical bacitracin ointment, hexachlorophene baths and rifampin by mouth with or without TMP/SMX was effective in eradicating MRSA colonization.[11] They evaluated the cases of 16 patients treated with rifampin with an 81% eradication rate and 26 patients treated with rifampin and TMP/SMX with 88% eradication. Follow-up cultures were obtained between the 2nd and 40th week after treatment and the number of follow-up cultures obtained was not noted. Rifampin resistance was found in two of three patients in whom therapy without TMP/SMX failed but in none of three who received combined therapy.

Based on this work we undertook an evaluation of combination oral therapy with rifampin and TMP/SMX in asymptomatic carriers of MRSA at a time when our hospital was undergoing an outbreak similar to those previously reported. In our institution we found that in vitro the epidemic strain was sensitive to all three antibiotics by agar diffusion testing, without antagonism noted. Unfortunately, initial suppression of MRSA was found in only 8 of 12 initial trials and 1 of 3 repeat trials. Clinical failure was partially predicted by the presence of a foreign body at the colonized site. With a five-day regimen, drug toxicity was not seen; however, drug-resistant isolates did occur when the protocol failed or was prolonged. Time-kill curves suggest that while TMP/SMX could prevent the development of rifampin resistance at serum concentrations, at lower antibiotic concentrations, which might be present at poorly vascularized sites, TMP/SMX did not prevent rifampin resistance in the epidemic strain tested.

Additionally, following early suppression of MRSA, there was in two patients asymptomatic recolonization with the epidemic strain without obvious cause. Relapse with resistant organisms did not occur in these patients. This suggests that a prolonged carrier state developed following colonization with MRSA and that this state was refractory to the oral regimen we used. It had not been anticipated that relapse could occur after the first month and, as most of our patients did not have prolonged follow-up, we could not establish the incidence of such persistence. Consequently, we feel that treatment with this rifampin/TMP/SMX regimen cannot be presumed to reliably eradicate the carrier state. Our results differ from those reported previously when this combination was used in conjunction with bacitracin ointment and hexachlorophene baths. The difference may relate to the lack of these topical agents in our protocol, more prolonged follow-up in our study or to the culturing techniques of a zealous infection control nurse who vigorously swabbed the skin surfaces of the patients on follow-up.

It is possible that the inability of oral antibiotic therapy to completely eradicate carriage may not preclude its usefulness in controlling nosocomial MRSA

outbreaks. We speculate that a transient decrease in MRSA colonization may have accounted for the fact that we did not recognize any secondary cases arising from contact with a patient treated with this protocol.

In this study we showed that rifampin and TMP/SMX have in vitro activity against MRSA. Clinically five days of combined therapy had only limited success in eradicating carriage of MRSA during a typical outbreak, but during our evaluation of the regimen this outbreak of MRSA infections resolved. This therapy should undergo further controlled investigations to establish its usefulness in the management of nosocomial MRSA outbreaks.

REFERENCES

1. Haley RW, Hightower AW, Khabbaz RF, et al: The emergence of methicillin-resistant *Staphylococcus aureus* infections in United States hospitals—Possible role of the house staff-patient transfer circuit. Ann Intern Med 1982 Sep; 97:297-308

2. Boyce JM: Nosocomial staphylococcal infections (Letter). Ann Intern Med 1981 Aug; 95:241-242

3. Locksley RM, Cohen ML, Quinn TC, et al: Multiply antibiotic-resistant *Staphylococcus aureus:* Introduction, transmission, and evolution of nosocomial infection. Ann Intern Med 1982 Sep; 97:317-324

4. Saravolatz LD, Pohlod DJ, Arking LM: Community-acquired methicillin-resistant *Staphylococcus aureus* infections: A new source for nosocomial outbreaks. Ann Intern Med 1982 Sep; 97:325-329

5. Watanakunakorn C: Treatment of infections due to methicillin-resistant *Staphylococcus aureus*. Ann Intern Med 1982 Sep; 97:376-378

6. Craven DE, Kollisch NR, Hsieh CR, et al: Vancomycin treatment of bacteremia caused by oxacillin-resistant *Staphylococcus aureus:* Comparison with β-lactam antibiotic treatment of bacteremia caused by oxacillin-sensitive *Staphylococcus aureus*. J Infect Dis 1983 Jan; 147:137-143

7. Thompson RL, Cabezudo I, Wenzel RP: Epidemiology of nosocomial infections caused by methicillin-resistant *Staphylococcus aureus*. Ann Intern Med 1982 Sep; 97:309-317

8. Crossley K, Landesman B, Zaske D: An outbreak of infections caused by strains of *Staphylococcus aureus* resistant to methicillin and aminoglycosides—II. Epidemiologic studies. J Infect Dis 1979 Mar; 139: 280-287

9. Peacock JE Jr, Marsik FJ, Wenzel RP: Methicillin-resistant *Staphylococcus aureus:* Introduction and spread within a hospital. Ann Intern Med 1980 Oct; 93:526-532

10. Methicillin-resistant *Staphylococcus aureus*—United States. MMWR 1981; 30:557-559

11. Ward TT, Winn RE, Hartstein AI, et al: Observations relating to an inter-hospital outbreak of methicillin-resistant *Staphylococcus aureus:* Role of antimicrobial therapy in infection control. Infect Control 1981 Nov-Dec; 2:453-459

12. Lennette EH, Balows A, Mausler WJ Jr, et al (Eds): Manual of Clinical Microbiology, 3rd Ed. Washington, DC, American Society for Microbiology, 1980, pp 83-87

13. Bauer AW, Kirby WM, Sherris JC, et al: Antibiotic susceptibility testing by a standardized single disk method. Am J Clin Pathol 1966; 45:493-496

14. Ericsson HM, Sherris JC: Antibiotic sensitivity testing—Report of an international collaborative study. Acta Pathol Microbiol Scand (B) 1971; 217(suppl):1-90

15. Steers E, Foltz EL, Graves BS, et al: An inocula replicating apparatus for routine testing of bacterial susceptibility to antibiotics. Antibiot Chemother 1959; 9:307-311

16. Zierdt CH: Long-term *Staphylococcus aureus* carrier state in hospital patients. J Clin Microbiol 1982 Sep; 16:517-520

17. Bryan CS, Wilson RS, Meade P, et al: Topical antibiotic ointments for staphylococcal nasal carriers: Survey of current practices and comparison of bacitracin and vancomycin ointments. Infect Control 1980 May-Jun; 1:153-156

18. Boris M: Bacterial interference: Protection against staphylococcal disease. Bull NY Acad Med 1968 Oct; 44:1212-1221

19. Drutz DJ, Van Way MH, Schaffner W, et al: Bacterial interference in the therapy of recurrent staphylococcal infections: Multiple abscesses due to the implantation of the 502A strain of staphylococcus. N Engl J Med 1966; 275:1161-1165

20. Maibach HI, Strauss WG, Shinefield HR: Bacterial interference: Relating to chronic furunculosis in man. Br J Dermatol 1969; 81(suppl 1): S69-S76

21. Sande MA, Mandell GL: Effect of rifampin on nasal carriage of *Staphylococcus aureus*. Antimicrob Agents Chemother 1975 Mar; 7:294-297

22. Wheat LJ, Kohler RB, White AL, et al: Effect of rifampin on nasal carriers of coagulase-positive staphylococci. J Infect Dis 1981 Aug; 144:177

23. Wilson SZ, Martin RR, Putman M, et al: Quantitative nasal cultures from carriers of *Staphylococcus aureus:* Effects of oral therapy with erythromycin, rosamicin, and placebo. Antimicrob Agents Chemother 1979 Mar; 15:379-383